



The effects of hydroalcoholic extracts of watermelon and Persian melon rind on kidney stone prevention in male Wistar rats: Alternative medicine and the role of physician and nurse

Leila Mahmood Nia^{1#}, Saba Najafi Dehkordi^{2#}, Majid Shirani³, Ali Hasanpour Dehkordi^{4*}

¹School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

²Students Researches Committee of Shahrekord University of Medical Sciences School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

³Department of Urology, Shahrekord University of Medical Sciences, Shahrekord, Iran

⁴Social Determinants of Health Research Center, School of Allied Medical Sciences, Shahrekord University of Medical Sciences, Shahrekord, Iran

Both authors contributed equally to this work.

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ABSTRACT

Introduction: Both watermelon and Persian melon extracts have various pharmacological properties like anti-diabetic, anti-viral, anti-cancer, and anti-urolithiasis effects.

Objectives: The present study was conducted to investigate the effects of hydroalcoholic extracts of watermelon and Persian melon rind on kidney stone prevention in male Wistar rats.

Materials and Methods: Fifty-six Wistar rats were randomly divided into seven groups and treated for 28 days. The first group (healthy control) and the second group (negative control) received drinking water and water containing 1% ethylene glycol, respectively. The third and fourth groups, received 100 mg/kg/d hydroalcoholic extract of watermelon rind and Persian melon rind, respectively in addition to 1% ethylene glycol. The fifth and sixth groups, received 400 mg/kg/d hydroalcoholic extract of watermelon rind and Persian melon rind, respectively in addition to 1% ethylene glycol. The seventh group received 0.5 mEq/kg/d potassium citrate in addition to 1% ethylene glycol for prevention and treatment of kidney stone. A 24-hour urine collection was conducted to determine the levels of sodium, calcium, uric acid, oxalate and citrate concentration. Histological study of calcium oxalate crystals was also performed. The serum levels of urea, creatinine, uric acid, calcium, phosphorus, magnesium, SGPT (serum glutamic-pyruvic transaminase), SGOT (serum glutamic-oxaloacetic transaminase), total antioxidant capacity, and malondialdehyde (MDA) of blood were determined accordingly.

Results: In the present study, administration of high-dose extract of watermelon and Persian melon rind (400 mg/kg/d) and potassium citrate showed significant changes in variables of sodium, calcium, uric acid, citrate, urine volume ($P < 0.01$), blood creatinine, blood uric acid, blood calcium, and serum SGPT ($P < 0.05$). The histological study of calcium oxalate crystals showed a significant reduction in oxalate levels in all prevention groups.

Conclusion: The extracts of watermelon and Persian melon rind are effective in preventing calcium oxalate stones by decreasing the levels of oxalate, sodium, and calcium and increasing citrate levels and urine volume and affecting the total antioxidant capacity. Persian melon rind extract was more effective than potassium citrate and watermelon rind extract in reducing urine sodium. High-dose watermelon rind extract showed similar effects as potassium citrate.

Implication for health policy/practice/research/medical education:

Natural extracts of watermelon and melon rind can be used in the prevention and treatment of kidney stones.

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Introduction

Kidney stones are considered as a global concern, which are not associated with race, gender, geography, or culture (1). The problem occurs more frequently in men than in women within the age range of 20–49 years (1-4). The increasing prevalence of kidney stone formation in age groups of <20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, and 60 years and older (0.27%, 3.15%, 5.96%, 8.18%, 9.14%, and 9.68%, respectively) show that it increases with age (5). Without using metaphylaxis, the relapsing rate of secondary stone formation is estimated to be 10–23% per year, 50% in 5–10 years, and 75% in 20 years of age (2). In Western countries, the lifetime prevalence is reported to be 10%–12% in men and 5%–6% in women (3). Although the etiology of kidney stone is not completely realized, various internal and external factors are involved in the occurrence of this disease. Internal factors include genetic history, age, gender, and diseases such as chronic gastroenteritis and hyperparathyroidism (2,3,6). Climate conditions, the amount of water consumed and the minerals that exist in the water, stress, diet, and medicines are among the external factors affecting the formation of ureteral stones (4,7).

Kidney stones are the third most common disease of the urinary tract after urinary tract infections and prostate disorders (2,8,9), and their prevalence is increasing in industrialized countries due to changes in people's lifestyle and dietary habits. Diet plays an important role in the formation of ureteral stones (2,10). Factors such as high consumption of animal protein, fat, salt, simple sugars, low consumption of fruits and vegetables (high-fiber foods), as well as low fluid intake increase the risk of ureteral stones (11,12). Obesity, inactivity, urinary incontinence, urinary tract infection, urethral stricture, taking certain medications, and increased concentration of calcium in the blood are also effective (11-13). Chemotherapeutic drugs, supportive techniques (including higher consumption of fluids, and acidic or alkaline solvents) and surgical methods including, ureteral obstruction surgery, extracorporeal shockwave therapy, transurethral lithotripsy, percutaneous nephrolithotomy and open surgery are the common methods for treatment (14,15). The side effects of chemotherapeutic drugs for kidney stones include nausea, itching, weight loss, jaundice, anuria, joint pain, and muscle weakness (2,5,11,16). The size of the stone is the most important factor in determining the treatment method (16).

In recent years, due to the numerous side effects of chemical drugs and surgical methods, researchers have turned their attention to herbal products. In Persian traditional medicine, different medicinal plants have been used to remove or dissolve kidney stones or prevent their formation (17). So far, several studies have shown the positive effects of some of these medicinal plants on animal models for kidney stone formation (18).

Melon (*Cucumis melo* L.) is a plant of the Cucurbitaceae genus (19). It has vitamins A and C and plays an important role in repairing and regenerating the body's cells. With highly diuretic property, melon is very useful for people who suffer from kidney disease and kidney stones (20, 21). Persian melon is rich in vitamins A and C and cellulose. It is also a laxative fruit and is very useful for the treatment of constipation (22). Watermelon, (*Citrullus vulgaris* Schrad.), a plant of the Cucurbitaceae genus (23) has anti-diabetic, antiviral, antimicrobial, and anti-cancer effects. So far, 17 compounds of watermelon have been identified, which are divided into five categories; alcohol, ketone, epoxy compounds, hydrocarbons, and acids (24–27). Watermelon and Persian melon are laxatives and are therefore effective in excreting waste materials and urine sediments. Research showed that Persian melon rind leads to smaller calcium oxalate crystal formation, which is easier for the urinary system to excrete. On the other hand, it prevents calcium oxalate crystals from sticking together and prevents the formation of the primary nucleus of the kidney stone, which increases the levels of calcium oxalate monohydrate crystals compared to control. Although the Persian melon rind mechanism of action in preventing the formation of large crystals has not been determined yet, this plant is recommended in Persian traditional medicine for the treatment of kidney stones (19,25,26,28). Studies showed that the white part of watermelon has a large amount of citrulline (a type of amino acid) that improves blood circulation by expanding the arteries. Watermelon rind contains less water and sugar but more fiber compared to the red flesh of the fruit. Therefore, the rind is tasteless. Unlike the red flesh of the watermelon, which contains antioxidants like lycopene, its white rind is rich in amino acids such as citrulline. In the urea cycle, citrulline combines with another acid to produce arginine. It relaxes blood vessels and contributes to the treatment of angina, cardiovascular disease, and kidney stones. Watermelon rind is widely used in traditional Chinese medicine to detoxify the body (29). Eidi et al found that the hydroalcoholic extract of Persian melon rind reduces the size of calcium oxalate crystals, facilitates their excretion by the urine, and possibly prevents the formation of the primary nucleus of the kidney stone a study showed the hydroalcoholic extract of watermelon rind increases small calcium oxalate monohydrate crystals and decreases large calcium oxalate monohydrate crystals. Hydroalcoholic extract of watermelon rind increases the number of calcium oxalate crystals. They also showed that a decrease in the size of calcium oxalate crystals facilitates their excretion by the urine (20). Despite recent investigations in this regard, no scientific study has been conducted on the effects of these fruits on kidney stones.

Objectives

The present study was conducted to investigate the effects

of hydroalcoholic extracts of watermelon and Persian melon rind on kidney stone prevention in male Wistar rats.

Materials and Methods

The present study is an in-vivo research conducted on 56 Wistar rats after obtaining approval from the Ethics Committee of Shahrekord University of Medical Sciences in 2019. The animals were randomly divided into seven groups.

Inclusion criteria

Male Wistar rats weighing 25-30 g.

Research variables

24-hour sodium, calcium, uric acid, oxalate, citrate, and urine volume. Urea, creatinine, uric acid, calcium, phosphorus, magnesium, SGPT (serum glutamic-pyruvic transaminase), SGOT (serum glutamic-oxaloacetic transaminase), total antioxidant capacity, and MDA (malondialdehyde) of blood. Histological study of calcium oxalate crystals.

Procedure

Preparation of hydroalcoholic extract and treatments

First, the rind was placed in a cool, shady area and was dried. The dried samples were ground by a mill and the hydroalcoholic extract (70% ethanol) was prepared by maceration extraction method.

For this research, 56 male Wistar rats weighing 250-300 g were housed in 12/12 hours light/dark cycle at 22-25°C and 50-60% humidity. Seventy-two hours before the beginning of the test, the rats were weighed and randomly divided into seven groups and treated for 28 days.

1. Rats in the first group had access to drinking water and food.
2. Rats in the second group had access to drinking water and 1% ethylene glycol.
3. Rats in the third group (prevention group with low-dose Persian melon rind extract) received drinking water that contained 1% ethylene glycol and 100 mg/kg body weight hydroalcoholic extract of Persian melon rind (29).
4. Rats in the fourth group (prevention group with low-dose watermelon rind extract) received drinking water that contained 1% ethylene glycol and 100 mg/kg body weight hydroalcoholic extract of watermelon rind (29).
5. Rats in the fifth group (prevention group with high-dose Persian melon rind extract) received drinking water that contained 1% ethylene glycol and 400 mg/kg body weight hydroalcoholic extract of Persian melon rind (29).
6. Rats in the sixth group (prevention group with high-dose watermelon rind extract) received drinking

water that contained 1% ethylene glycol and 400 mg/kg body weight hydroalcoholic extract of watermelon rind (29).

7. Rats in the seventh group (prevention group with 0.5 mEq/kg/d potassium citrate) received drinking water that contained 1% ethylene glycol and 0.5 mEq/kg/d potassium citrate (27).

Collection and evaluation of urine samples

For 24-hour urine collection, the rats were individually kept in metabolic cages on days zero, 14, and 28. After 24 hours, the volume of urine collected from each rat was measured and 10 mL of the urine was transferred to a tube containing 25- μ L hydrochloric acid and the lid was sealed with parafilm. The biochemical analysis of urine was performed at the university's reference laboratory. Enzyme assay kits were used to measure urine oxalate and citrate, while the colorimetric xylydyl blue method was used to measure urine calcium. Urine biochemistry, urine volume, and the levels of oxalate, citrate, calcium, phosphorus, creatinine, and uric acid were also examined. Enzyme assay kits were used to measure urine oxalate and citrate, and colorimetric xylydyl blue method was used to measure urine calcium.

Preparation and evaluation of serum

Blood samples in each group were collected by heart sampling on day zero and on day 29. Blood samples were centrifuged after clotting, and the serum was collected at this stage and biochemical studies were performed. Measuring serum calcium and magnesium was done by colorimetric xylydyl blue and methylthymol blue methods, respectively. Blood urea nitrogen, creatinine, SGOT, SGPT, MDA, calcium, phosphorus, and uric acid tests were also performed.

Preparation and pathological examinations of renal tissue

After the treatment of rats, each rat was anesthetized on day 29, and each pair of kidneys was fixed in a container containing 10% formalin and pathological examinations were performed on them. After preparing the tissue sections, the samples were transferred to the automatic tissue processing machine for dehydration, clearing alcohol from tissues, and infiltration with paraffin. Then, 5 μ sections were prepared and placed in an autoclave at 180°C for 15 minutes. In the last step, the sections were placed on gelatinous slides, and stained with hematoxylin and eosin. After observing the slides under the microscope, calcium oxalate crystals, which were observed in the form of yellow to brown crystal aggregations in the renal tubule, were examined and counted in ten microscopic fields.

Measurement of serum antioxidant capacity

Measurement of serum antioxidant capacity was done by

the ferric reducing antioxidant power method.

Statistical analysis

In this study, the data were analyzed using SPSS 19 software by analysis of variance (ANOVA) and Tukey's (Post Hoc) tests. Statistical significance for comparisons was defined as $P < 0.05$.

Results

According to Table 1, urine sodium in groups 5, 6, and 7 had a significant decrease compared to the healthy control group and the negative control group ($P < 0.05$). However, the effect of low-dose hydroalcoholic extract of watermelon rind and Persian melon rind was not significantly different from the healthy control group and the negative control group. Urine calcium in different groups showed a significant decrease compared to the healthy control group and the negative control group ($P < 0.05$). Urine oxalate in the groups receiving potassium citrate and high-dose hydroalcoholic extracts of watermelon and Persian melon rind (groups 5, 6, and 7) was significantly less than the negative control group (group 2). Other groups did not show a significant difference compared to the healthy control group and the negative control group. The hydroalcoholic extract of watermelon rind and Persian melon rind did not affect urine citrate. In addition, the extract of watermelon rind and Persian melon rind had positive effects in increasing the urine volume of rats compared to the negative control group. The results show that high-dose watermelon rind

extract decreased creatinine and had beneficial effects.

The extract of watermelon rind and Persian melon rind and potassium citrate do not affect blood urea, SGPT, SGOT, magnesium, and MDA, but they affect phosphorus, yet this effect is not statistically significant.

Adding ethylene glycol to drinking water increased urine oxalate in rats. In prevention groups that, in addition to ethylene glycol, received the extract of watermelon and Persian melon rind (high doses) as well as potassium citrate, urine oxalate levels decreased significantly.

To study the morphological changes of the kidney, we prepared 4- μm -thick sections, which were stained with H&E (hematoxylin and eosin) staining. We found that group one has a normal kidney as shown in Figure 1A. Renal tubules in group 2 had abundant oxalate crystals that occupied most of the tubules (Figure 1B), while group 3, which was treated with 100 mg/kg Persian melon in addition to ethylene glycol, showed normal renal tissue and tubules without oxalate crystals (Figure 1C). Accordingly, rats in group 4 were treated with 100 mg/kg watermelon in addition to ethylene glycol, and showed normal renal tissue and tubules without oxalate crystals (Figure 1D). Likewise, rats in groups 5 and 6 were treated with 400 mg/kg Persian melon and 400 mg/kg watermelon in addition to ethylene glycol, and showed normal kidney tissue and tubules without oxalate crystals (Figures 1E and 1F). However, in group 7 in which rats were treated with potassium citrate and ethylene glycol, we found a 20% improvement of renal tubules in oxalate formation (Figure 1G).

Table 1. Variance analysis of urine tests

		Sum of squares	df	Mean square	F	P value
Urine sodium (mmol/day)	Between groups	61.95	6	10.32	6.54	<0.03
	Within groups	72.56	46	1.57		
	Total	134.51	52			
Urine calcium (mg/24 h)	Between groups	3.92	6	0.652	9.01	<0.014
	Within groups	3.32	46	0.07		
	Total	7.24	52			
Uric acid urine (mg/24 h)	Between groups	12.72	6	2	13.63	<0.02
	Within groups	7.15	46	0.155		
	Total	19.87	52			
Urine Oxalate (mg/24 h)	Between groups	86.62	6	14.43	14.31	<0.02
	Within groups	46.40	46	1.00		
	Total	133.03	52			
Urine citrate (mg/24 h)	Between groups	79.53	6	13.25	7.54	<0.04
	Within groups	80.86	46	1.76		
	Total	160.39	52			
Urine volume (mL/24 h)	Between groups	1368.43	6	228.07	5.17	<0.03
	Within groups	2027.71	46	44.08		
	Total	3396.14	52			

Discussion

The results of the present study showed that the consumption of watermelon rind and Persian melon rind extract and potassium citrate influences the variables of urine sodium, calcium, uric acid, urine citrate, and urine volume and is effective in preventing calcium oxalate stones. Although the mechanism of action of watermelon rind and Persian melon rind in preventing the formation of large crystals has not been determined yet, this plant is recommended in Persian traditional medicine for the treatment of kidney stones (25,26). In laboratory studies, the effects of watermelon rind extract on calcium oxalate stone have been shown. A study by Eidi et al on the effect of different concentrations of watermelon rind extract in preventing crystallization of calcium oxalate under in vitro conditions showed that different concentrations of hydroalcoholic extract of watermelon rind increased the percentage of small crystals and decreased the percentage of large crystals. On the other hand, this extract increased the small calcium oxalate monohydrate crystals. Additionally, the hydroalcoholic extract of watermelon rind has increased optical absorption and increased the number of calcium oxalate crystals (20). Studies in recent decades have shown an increase in calcium oxalate and a decrease in urine citrate in rats with kidney stones (30). Citrate is the most important ingredient in ureteral stones. Citrate binds to calcium in the urine, prevents calcium from reaching saturation and thus, prevents crystallization of calcium (31-33). The study showed that different concentrations of hydroalcoholic extract of watermelon rind increase the percentage of small 5-5.2 μm and 6-9 μm crystals and decrease the percentage of large 17-21 μm , 22-30 μm and 31-40 μm crystals. On the other hand, the hydroalcoholic extract of watermelon rind increases small calcium oxalate monohydrate crystals and decreases large calcium oxalate monohydrate crystals (20,25,27). In the present study, adding 1% ethylene glycol to drinking water caused high levels of oxalate, sodium, calcium, uric acid, and low urine volume and urine citrate, indicating the presence of calcium oxalate stones in the rats. In this study, the prevention and excretion of calcium oxalate stones by watermelon rind extract decreased the

levels of urine oxalate, urine sodium, urine calcium, uric acid and increased the levels of citrate and urine volume. Furthermore, after 28 days of intervention by watermelon rind extract creatinine and calcium did not decrease significantly compared to control groups. However, watermelon rind extract had little effect on phosphorus, magnesium, MAXIFER, SGPT, MDA, and SGOT in the blood. Histological study of calcium oxalate crystals also indicates the absence of calcium oxalate in the treated rats. The results of the study of Eidi et al showed that hydroalcoholic extract of Persian melon rind increases the small calcium oxalate monohydrate crystals and decreases the large calcium oxalate monohydrate crystals. Furthermore, the hydroalcoholic extract of Persian melon rind facilitates the excretion of calcium oxalate crystals by the urine through decreasing the size of calcium oxalate crystals and possibly prevents the formation of the primary nucleus of the kidney stone (20). Gupta et al proposed the plant *Crateva adansonii* to prevent the formation of calcium oxalate stones in rats (34). Consistent with the results of the present study, the results of these studies indicate the positive effect of traditional medicinal plants in the prevention and excretion of kidney stones. In the present study, consumption of high-dose Persian melon rind extract (400 mg/kg) showed significant effects on urine sodium, calcium, uric acid, citrate, and urine volume in the prevention of calcium oxalate stones. However, it did not affect blood factors such as urea, creatinine, uric acid, calcium, phosphorus, magnesium, SGPT, SGOT, total antioxidant capacity, and MDA. The histological study of calcium oxalate crystals also shows a significant reduction in oxalate levels. In the present study, the effects of hydroalcoholic extract of watermelon rind and Persian melon rind were compared with the effects of potassium citrate on calcium oxalate stone for the first time. According to the results, the extract of watermelon and Persian melon rind and potassium citrate showed similar effects on the prevention of kidney stones in rats, which was associated with decreased oxalate, sodium, calcium, uric acid, and increased citrate and urine volume. Antimicrobial, pharmacological, urine enhancing (kidney, bladder, and liver cleansing) and immune system

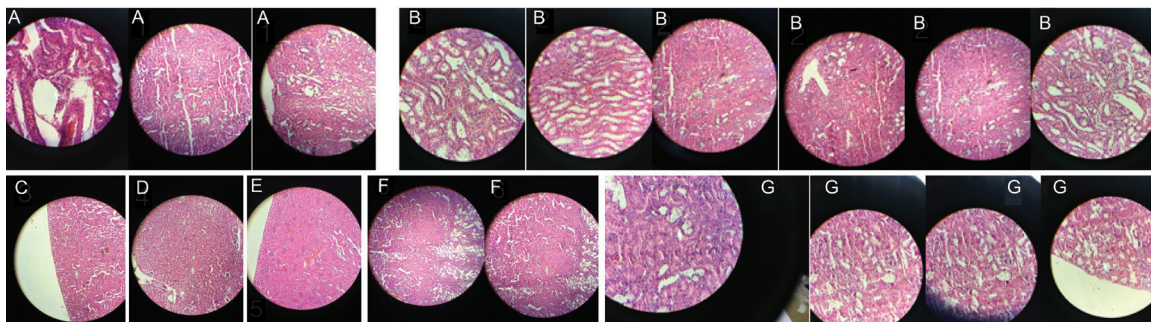


Figure 1. The histological view of calcium oxalate crystals.

boosting properties may play a role in the development of such effects. Histological study of calcium oxalate crystals also indicates the absence of calcium oxalate in all treatment groups. It is recommended that the efficacy and safety of watermelon rind extract capsules be evaluated by determining hepatic, hematologic, and renal factors in patients.

Conclusion

According to the results of this study, Persian melon rind extract has better effects than potassium citrate and watermelon rind extract in reducing urine sodium, and the effects of high-dose watermelon rind extract are similar to potassium citrate. The extract of watermelon rind and Persian melon rind is effective in preventing calcium oxalate stones by reducing the amount of oxalate, sodium, calcium, and increasing citrate and urine volume and affecting the total antioxidant capacity.

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Authors' contribution

LM, SN, and AHD were the principal investigators of the study. MSH, AHD, and LM were included in preparing the concept and design. AHD and MSH rechecked the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical issues

This experimental protocol was performed according to the regulations of the Research Ethics Committee of Iranian Ethical Guidelines for the use of animals in research. Additionally, all animal experiments were under protocols approved by the United States National Institutes of Health (NIH, 1978). This study was also approved by the ethics committee of Shahrekord University of Medical Sciences (Ethical#IR.SKUMS.REC.1397.40). This study was extracted from the M.D thesis of Saba Najafi Dehkordi at the department of general medicine. Faculty of medicine of this university. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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